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Anti-inflammatory activity of benzophenone and xanthone derivatives isolated from *Garcinia* (Clusiaceae) species

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ABSTRACT

Species of the genus *Garcinia* have been the source of many benzophenone and xanthone derivatives. Recent data regarding potent biological properties of natural compounds in *Garcinia* species led us to investigate the *in vitro* anti-inflammatory effect of three known xanthones, lichexanthone (**1**), 1,3,6,7-tetrahydroxyxanthone (**2**), 1,3,5,6-tetrahydroxyxanthone (**3**), two new xanthones 1-hydroxy-3,6,7-tri-*O*,*O*,*O*-triprenylxanthone (**4**), 1,6-dihydroxy-3,7-di-*O*,*O*-diprenylxanthone (**5**) and two benzophenones isoxanthochymol (**6**), guttiferone E (**7**), isolated from *Garcinia nobilis* and *Garcinia punctata*. The Griess assay was used for the measurement of nitric oxide (NO) production in RAW264.7 macrophages and the ferrous oxidation-xylenol orange assay was used to determine the 15-lipoxygenase (15-LOX) inhibitory activity. All the compounds had inhibitory effect on 15-LOX activity to different extents. Compound (**7**) had the highest anti-LOX activity with an IC_{50} value of 43.05 μg/mL. At the highest studied concentration (25 μg/mL), compound (**4**) had the most potent inhibitory activity against NO release with a% of inhibition of 95.42% and less cytotoxic effect on RAW264.7 cells (% of cell viability of 81.40).

The results presented here suggest that 1,3,5,6-tetrahydroxyxanthone (**3**) and guttiferone E (**7**) are promising inhibitors of NO production and 15-LOX activity. Further studies should be considered in order to elucidate the mechanism by which these compounds exert their inhibitory activities.

1. Introduction

Natural products, particularly, plant products have been associated with therapeutic properties for various diseases since ancient times. There is an increasing interest in natural product research due to the failure of alternative drug discovery methods to deliver many lead compounds in key therapeutic areas such as inflammation and other metabolic diseases (John, 2009). Inflammation is now recognized as an overwhelming burden to the healthcare status of human populations and the underlying basis of a significant number of diseases (Edwards, 2005). Although several drugs are available for these conditions, many of the currently available anti-inflammatory drugs have considerable side effects that limit their clinical use (Viola et al., 2008). There is therefore demand for more effective and safe anti-inflammatory drugs. The immune system is frequently involved with inflammatory disorders. Macrophages are key players in various inflammatory diseases and in the immune response where they release pro-inflammatory mediators and proteins, including nitric oxide and leukotrienes the end products of lipoxygenases (LOX) (Homaidan et al., 2002).

Natural product research continues to explore a variety of lead structures, which may be useful as templates for the development of new drugs (Harvey, 2000). Therefore, investigation of natural product inhibitors of pro-inflammatory mediators and enzymes such as NO and LOX could be an alternative in the discovery of new therapeutic agents against inflammatory diseases. The genus *Garcinia* is the largest of Clusiaceae (or Guttiferae) family about 400 species widely distributed in tropical Asia and Africa. Some species such as *Garcinia mangostana* have anti-inflammatory, antinociceptive and antipyretic activities (Chen et al., 2008). *Garcinia* species are known to contain a wide variety of oxygenated

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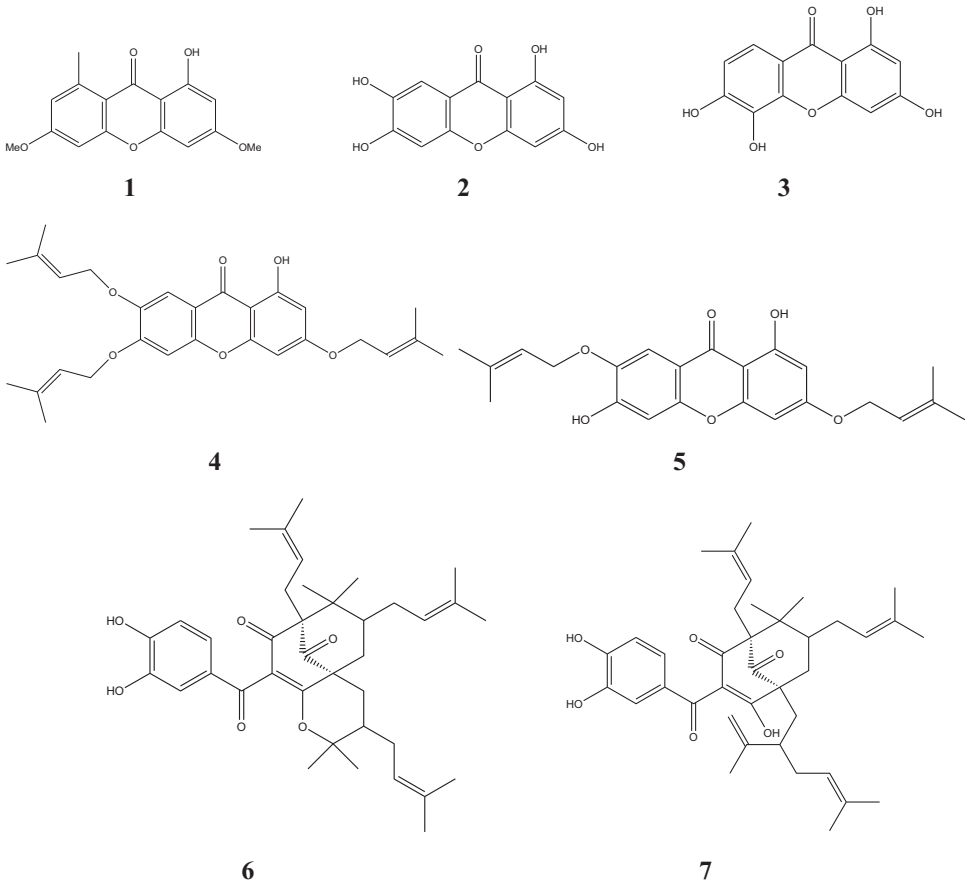

Fig. 1. Chemical structures of lichexanthone (**1**), 1,3,6,7-tetrahydroxyxanthone (**2**), 1,3,5,6-tetrahydroxyxanthone (**3**), 1-hydroxy-3,6,7-tri-*O*,*O*,*O*-triprenylxanthone (**4**), 1,6-dihydroxy-3,7-di-*O*,*O*-diprenylxanthone (**5**), isoxanthochymol (**6**), guttiferone E (**7**).

and prenylated xanthones, as well as polyisoprenylated benzophenones such as the guttiferones (Nguyen et al., 2005). Benzophenone and xanthone derivatives such as mangostin, isomangostin and mangostin triacetate isolated from *Garcinia* species have good anti-inflammatory activity (Lin et al., 1996; Zhang et al., 2014). Nevertheless, there are limited scientific reports on benzophenone and xanthone derivatives as possible inhibitors of LOX and NO production. As part of our continued search for biologically active compounds from plants against inflammatory conditions, the present study was aimed at evaluating the anti-LOX activity and NO production inhibitory effect of five benzophenones and xanthones derivatives isolated from two Cameroonian medicinal plants *Garcinia nobilis* Engl. and *Garcinia punctata* Oliv and two new semisynthetic xanthone derivatives.

2. Results and discussion

2.1. Isolated compounds

The structures of the isolated compounds and those from the chemical transformation were elucidated on the basis of spectroscopic data (EIMS, ^{1}H NMR and ^{13}C NMR, HSQC, HMBC) Fig 1). By comparison of the data with those reported in the literature, three compounds were identified as lichexanthone (**1**) (Pettit et al., 2004); 1,3,6,7-tetrahydroxyxanthone **(2)** (Fouotsa et al., 2014) and 1,3,5,6-tetrahydroxyxanthone **(3)** (Fouotsa et al., 2014), isoxanthochymol **(6)** and guttiferone E **(7)**. Compound **4** and **5** were obtained by semisynthesis of compound **2** and elucidated using NMR spectral data as 1-hydroxy-3,6,7-tri-*O*,*O*,*O*-triprenylxanthone and 1,6-dihydroxy-3,7-di-*O*,*O*-diprenylxanthone respectively.

2.2. Inhibition of NO production

The Griess agent was used to determine the inhibition of compounds on LPS-induced NO production in RAW264.7 cells. The treatment of RAW264.7 cells with LPS resulted in a statistically significant increase of nitrite concentration in the medium compared to non-treated control (Fig. 2). Unstimulated

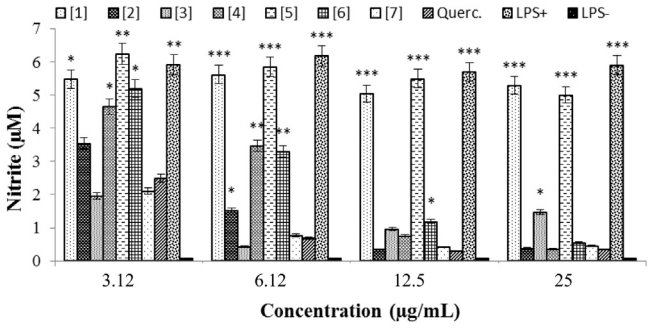

Fig. 2. Inhibitory activity of benzophenone and xanthone derivatives on nitric oxide in LPS-activated RAW 264.7 macrophages determined by the amount of nitrite production inhibition after co-incubation with LPS 1 µg/mL for 24 h. (Querc: quercetin). Data represent the mean ± SD of three independent experiments $^{*}p < 0.05$, $^{*}p < 0.01$ and $^{***}p < 0.001$ are significantly different from the reference compound quercetin.